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Profile of Drug Resistant Gram Negative Bacteria from ICU at a Tertiary Care Center of India

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Authors' contributions

This work was carried out in collaboration between all authors. Authors AA and SS designed the study. Author AA undertook all the experimental procedures. All authors were involved in data collection, statistical analysis and literature searches. Authors CJ and SS managed the analyses of the study. Authors CJ and AA wrote the first draft of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Infections are one of the most serious and dreaded complication in hospital settings especially for patients admitted in Intensive Care Units. Risk factors like decreased immunity and prevalence of multidrug resistant organisms in the surroundings along with multitude of drugs administered predispose the patient to infections. To formulate policies that are critical to effective treatment of such infections and prevent development of antibiotic resistance, there should be data of bacterial etiologies and infection patterns.

Aims: Detection of MDR pathogens like *Enterobacteriaceae* and *Acinetobacter* spp as indicator of assessing the cleanliness and adherence to basic standard infection control and prevention procedures. The study determines the prevalence and microbiological profile of MDR pathogens in ICU.

Methodology: This prospective study was conducted at Lady Hardinge Medical College and associated tertiary hospital, New Delhi between January and December 2016. A total of 158 clinical

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specimens were collected from the ICUs and analyzed by standard microbiological methods, disc potentiation and modified hodge test for the identification of ESBL-producing and carbapenemases production respectively.

Results: Out of 158 ICU isolates analysed, 104(65.8%) were from the Family *Enterobacteriaceae* with *Escherichia coli* being the predominant. Among the Genus *Acinetobacter* 54(34.4%), *A. baumannii* was 40(74.1%) and *A. lwoffii* 10(25.9%). Distribution among 104 isolates of *Enterobacteriaceae* submitted was: *E. coli* 42(26.5%), *Klebsiella spp* 52(32.9%) and *Proteus spp* 10(6.3%). Prevalence of ESBL producing was 22.7% and carbapenemases positive -9.6%.

All the pathogens were sensitive to colistin,

Low resistance was observed with *E. coli*, moderate resistance with gentamicin ranged from 14.3% to 59.2%, and High resistance observed with Amoxicillin-Clavulanate, piperacillin-tazobactam, meropenem and imipenem.

Conclusion: The study finding has revealed the presence of MDR pathogens with ESBL and carbapenemases enzymes capable of compounding patient management and infection control measures.

Keywords: ESBL; MHT; Acinetobacter; carbapenems.

ABBREVIATIONS

ATCC : American Type Culture Collection
CLSI : Clinical and Laboratory Standards Institute
ESBL : Extended Spectrum Beta Lactamases
GNB : Gram Negative Bacteria
ICU : Intensive Care Units
MBL : Metallo Beta Lactamases
MDR : Multi Drug Resistance
MHT : Modified Hodge Test

1. INTRODUCTION

The prevalence of Multi Drug-Resistant (MDR) Gram negative bacilli (GNB) is on the rise worldwide, posing a major public health threat. [1-3] In 2012, the Director of WHO raised the concern regarding the paucity of replacement antibiotics especially for Gram negative bacteria. Gram-negative bacteria are largely responsible for ICU-acquired infections which lead to higher ICU-mortality rates, increased morbidity and increased healthcare costs, while only limited therapeutic options are available [1].

This rising trend may lead to almost untreatable infections. β-Lactam antibiotics (penicillin's, cephalosporin's, monobactams, and carbapenems) are the safest and mostly widely used class of antibiotics ever developed. Their indiscriminate use creates a selective pressure which leads to the selection of multidrug resistant strains of organism [4]. Resistance to β-lactam antibiotics occurs primarily through the production of β-lactamases, enzymes that inactivate these antibiotics by splitting the amide bond of the β-lactam ring [5,6].

Prevalence of ESBL producing organisms lead to the use of carbapenems. This trend favored the emergence of carbapenem resistant bacteria. The most important resistance mechanism for carbapenems is the production of carbapenems hydrolyzing enzyme, metallo-β-lactamase (MBL), notably the *Klebsiella pneumoniae* carbapenemase (KPC) and metallo-β-lactamases (MBLs), such as the New Delhi metallo-β-lactamase (NDM) [6].

Lack of standardized method of detection for ESBL and MBL mediated resistance for GNB other than those belonging to family *Enterobacteriaceae* in clinical microbiology laboratory presents a problem.

A major challenge in the diagnosis of resistance is the presence of different classes of β lactamases in an isolate which prevents the accurate assessment of β lactamase producing strains in the high risk areas [1-3]. Bacterial antibiotic resistance once developed is slow or difficult to reverse along with the fact that the therapeutic options for the control of such are also limited. Thus to influence the spread of resistance, special measures like surveillance and monitoring have to be undertaken to detect the pattern of antibiotic sensitivity especially in areas like ICUs which are reservoirs and disseminating point for MDR pathogens within hospital environment and community. It is reasonable to say that acquisition of timely information and data may help in implementation of correct measures to control emergence of resistance and outbreaks.

Therefore the present study aimed to determine the prevalence rates of the multidrug resistant

Enterobacteriaceae and Acinetobacter which produced ESBL and Carbapenemase enzymes in various ICUs of a tertiary care center.

2. MATERIALS AND METHODS

The prospective observational descriptive study was carried out in the Department of Microbiology of a tertiary care hospital (Lady Hardinge Medical College and associated Hospital, Delhi). All isolates from various clinical samples sent for routine culture and sensitivity (except blood, urine and stool) as part of patient care from January to December 2016 were included in the study.

Repeat isolates with the same antibiogram from the same patient were excluded from the study. One hundred and fifty-eight isolates were from different ICUs.

The isolates were identified by standard bacteriological techniques [7]. VITEK ®(bioMérieux) was used to confirm different isolates.

2.1 Antimicrobial Susceptibility Tests

2.1.1 Disk diffusion tests

All identified strains were tested for antimicrobial susceptibility by Kirby-Bauer method on Mueller Hinton Agar (MHA) medium according to criteria recommended by Clinical and Laboratory Standards Institute (CLSI) [6]. Following antimicrobial agents (Hi-Media) were used for antibiotic susceptibility testing (potency in µg/disc): Amikacin (30), Amoxicillin-Clavulanate (20/10), Ceftriaxone (30), Colistin (10), Piperacillin-Tazobactam (100/10), Ciprofloxacin (5), Gentamicin (10), Imipenem (10) and Meropenem (10), Ceftazidime (30) and Ceftazidime-Clavulanate (30/10).

2.1.2 Detection of the ESBLs

E. coli and *Klebsiella* species were first screened for the production of ESBL by the Disk diffusion method using Ceftazidime and later on confirmed by the disk potentiation test using Ceftazidime-clavulanate. A difference of 5 mm or more in the zone diameters of cephalosporin disc and their cephalosporin/Clavulanate disk is taken to be phenotypic confirmation of ESBL production. The reference strains, ESBL positive *Klebsiella pneumoniae* ATCC 700603 and ESBL negative Escherichia coli ATCC 25922 were included in the study as controls [8,9].

2.1.3 Screening of carbapenems resistance

Screening of clinical isolates of *E. coli* and *Klebsiella* species was performed with Meropenem disk (10 ug) (Hi-media, Mumbai, India). The isolates showing a reduced susceptibility to Meropenem (zone diameter <21 mm) were presumed as positive. These positive isolates were subjected for confirmation of carbapenemases by Modified Hodge Test(MHT) by CLSI [8]. *Klebsiella pneumoniae* ATCC BAA 1705 and ATCC BAA 1706 were used as positive and negative control [8].

3. RESULTS

Of the 158 isolates analysed, 104(65.8%) identified as member of the family Enterobacteriacae, *Klebsiella* species (32.9%), *E. coli* (26.5%) and Proteus spp (6.3%). 54(34.1%) belongs to *Acinetobacter* spp.

In the Genus *Acinetobacter*, 25.31% (40) were *Acinetobacter baumannii* and the rest were *Acinetobacter lowffii* 8.9% (14).

Table 1. Distribution of isolates according to source

89 organism	ICU
E. coli	42(26.5%)
Klebsiella	52(32.9%)
Proteus	10(6.3%)
Acinetobacter	54(34.1%)

More than 60% of the isolates were from the respiratory specimens including sputum, endotracheal aspirates, broncho alveolar lavage and pleural fluid. Antibiogram of the ICU isolates were analyzed for detecting Multi drug resistant. All isolates from ICUs were tested for the presence of ESBL and MBL production.

All the isolates were sensitive to colistin. Among the isolates*, E. coli* demonstrated low resistance pattern to all the drugs tested. Moderate resistance pattern observed against gentamicin ranging from 14.3% to 59.2%. High resistance pattern observed with amoxicillin-clavulanate (61.9%-88.5%), piperacillin-tazobactam (33.3%-77%). Alarmingly high amikacin resistance in both *Klebsiella* and *Acinetobacter* species was detected. All isolates *of Proteus* species were resistance to ciprofloxacin.

Table 2. Antibiogram showing resistance phenotype in ICU isolates

Drug	*E. coli* (42)	*Klebsiella* (52)	*Proteus* (10)	*Acinetobacter* (54)
Amoxicillin-clavulanate	26 (61.9%)	46 (88.5%)	8 (80%)	NA
Piperacillin-tazobactam	14 (33.3%)	38 (73.1%)	0 (0%)	42 (77.7%)
Cefotaxime	10 (23.8%)	36 (69.2%)	10 (100%)	42 (77.7%)
Gentamicin	6 (14.3%)	24 (46.2%)	0 (0%)	32 (59.2%)
Amikacin	12 (28.6%)	42 (80.7%)	6 (60%)	44 (81.4%)
Ciprofloxacin	16 (33.3%)	44 (84.6%)	10 (100%)	46 (85.1%)
Meropenem	12 (23.8%)	38 (73.1%)	6 (60%)	38 (70.3%)
Imipenem	24 (57.1%)	44 (84.6%)	4 (40%)	50 (92.5%)
Colistin	0 (0%)	0 (0%)	NA	0 (0%)

Table 3. Prevalence of colistin sensitive, ESBL and MHT positive isolates

Organism	MDR isolates sensitive only to colistin	ESBL	MHT
E. coli (42)	4 (9.5%)	20 (47.6%)	8 (19.1%)
Klebsiella (52)	22 (42.3%)	8 (15.4%)	2 (3.8%)
Proteus (10)	0 *	0	0
Acinetobacter (54)	30 (55.5%)	8 (14.8%)	NA

MDR: Multidrug resistance
**Intrinsically resistant to colistin*

ESBL production was identified in 36 isolates in total *with E. coli* having majority of share followed by *Klebsiella* species and *Acinetobacter* spp. Ten (9.6%) isolates (8 *E. coli* and 2 *Klebsiella* species) confirmed as Carbapenemases Producing *Enterobacteriaceae*.

Fifty-five percent of *Acinetobacter* isolates were found to be MDR which were sensitive only to Colistin. However only 14.8% isolates among those were ESBL positive indicating other mechanism of resistance like porin loss.

4. DISCUSSION

Concern is warranted about the failure of present day antimicrobials to control the multi drug resistant microorganisms. The rapid emergence of infections which are caused by bacilli that produce various β lactamase enzymes have been reported with an increasing frequency in the ICUs and they are associated with a significant morbidity and mortality [1].

The numerous β- lactamases are encoded either by the chromosomal genes or by the transferable genes which are located on the plasmids or the transposons [5,6].

Such bacteria pose a definite risk to the ongoing efforts of infection control. ICUs are the high risk areas associated with patients requiring special care. They commonly have multiple invasive devices for various reasons like drug administrations or monitoring. Post-surgical patients usually have breach in anatomic barrier exposing them to environmental sources of infections.

In our study, the high rate of MDR strains in ICU suggest a possible transfer of genetic element carrying resistance genes. Higher prevalence of GNB in Inpatient setting was seen as compared to OPD. Possibly this could result from the higher prevalence of Gram positive cocci infection in OPD setting. The high prevalence of GNB resistant to 3rd generation cephalosporin in our study may be due to indiscriminate use of third generation cephalosporins to empirically treat Gram negative infections and also absence of antibiotic stewardship program [10].

In our study, the prevalence of various ESBL in the GNB, (*Enterobacteriaceae* & *Acinetobacter*) was 22.8%(36/158). Similar findings were reported in a study which was done by Laghawe et al. which reported 19.67% ESBL producers [11]. Another study in Qatar reported 17.3 % ESBL producers from intensive care unit [12]. Studies which were done by Harakuni et al. and Bandekar et al. reported high prevalence of the ESBLs (74%)in ICU and 39.8% in Burns patients [13,14].

Worldwide ESBL prevalence data show a great variation ranging from 10 to 80 % [15-18]. Low levels of ESBL could be due to complete absence of any zone of inhibition on the Muller Hinton agar plate, thus, hampering identification of ESBL producers using phenotypic methods.

The prevalence of carbapenemases production among GNB varies greatly according to country and among different institutions within the country. In the present study, 57.7% (56/104) of clinical isolates of *Enterobacteriaceae* were found to be MRP screen positive. Resistance to Meropenem was found to be more in *Klebsiella* species (73.1%) than in *E. coli* (23.8%) (Table 2). A high prevalence of resistance to carbapenems 14.64% in *E. coli* and 29.64% in Klebsiella species has been reported in study by Chauhan K et al, in hospital isolates from various in and outpatient areas [19]. Prevalence of resistance to carbapenems 2-13% in *E. coli* and 31-51% in *Klebsiella* species has been reported from a study by Wattal C et al in Delhi [20]. Another study by Gupta E et al. has reported carbapenems resistance (17-22%) in different strains of *Enterobacteriaceae* from North India [21]. Resistance to carbapenems are mediated by one or more of four mechanisms: enzymatic degradation, diminished permeability due to absence of OprD in GNB, efflux of drug across the outer membrane and production of altered PBP target.

In the study, imipenem resistance was higher than meropenem resistant in all GNB except Proteus species Study by Sumita Y suggested a new pathway for the translocation of meropenem other than that mediated by OprD2 across the outer membrane thus helping in entry of drug molecules in the presence of OprD mutation [22]. Our study isolated around 19.1 percent *E. coli* and 3.8 percent *Klebsiella* species to be Modified Hodge Test (MHT) positive. The MHT and Carba NP test is recommended by CLSI for the detection of carbapenemases in *Enterobacteriaceae*. However, MHT may give false positive results or fail to detect metallo β-lactamases (MBLs). In the US, MHT is the most widely used test for detection of carbapenemases and has been found to have a sensitivity and specificity of >90% for blaKPC producers. However, in India, the prevalence of blaNDM is higher than blaKPC producers [23]. Most patients admitted at a tertiary care center such as Lady Hardinge Medical College are referral cases which have received antibiotics from other hospitals or doctors prior to their admission. This could partly explain the high occurrence of carbapenemases producers in our setting. Carbapenemases production is usually accompanied by multiple resistance mechanisms resulting in an extensively drug-resistant profile [24].

A significant number of isolates were sensitive only to colistin, i.e., *E. coli* 9.5%, *Klebsiella* species 42.3% and *Acinetobacter* species 55.5%. Colistin has become the backbone agent in the treatment of CPE, typically in combination with other antibiotics. There is a grave concern regarding the isolation of emergence of Colistin resistant strains. According to national survey on carbapenemases-producing isolates recovered in 2014 discovered a high rate of colistin resistance in *Klebsiella pneumoniae* and Enterobacter cloacae (6.2% and 7.7%, respectively) in France [25]. MDR colonized/ infected patients should be isolated individually or in groups and treated in accordance with strict infection control directives. Fosfomycin has been shown to retain activity against these virulent pathogens, there is renewed interest in its use as a therapeutic agent [26]. MDR *Acinetobacter* baumannii colonization is associated with prolonged hospitalization, increased medical costs, and an increased mortality rate in the ICU [1]. Limitation of the study was unavailability of clinical data about the pattern of antibiotic usage in ICUs that could help reach a hypothesis of resistance development under drug pressure. Information regarding drug prescribing habits of clinicians and resistance phenotype in a given setting like ICU can help in rectifying the core problem of antibiotic misuse and subsequently prevent spreads of superbugs.

5. CONCLUSION

In conclusion, increasing prevalence of MDR resistance along with dependence on limited drugs can finally lead to pan drug resistant isolates. The study illustrates this rising concern depicting the vast number of ICU isolates of gram negative bacteria showing multidrug resistance. The antibiogram pattern of *Klebsiella* and *Acinetobacter* isolates shows higher resistance to commonly used antibiotics. Last resorts like colistin should be reserved to prevent emergence of resistance to them. The present study illustrates the need of a documented hospital infection control policy for prevention of emergence of resistance and thus right patient management approach.

The combinations therapy should be used empirically to broaden the antibacterial spectrum and treatment of severely ill patients at risk of infection with multidrug-resistant pathogens. Clinicians must strive to use carbapenems and other broad spectrum antibiotics judiciously in order to prolong the lifespan of these valuable drugs. Rapid diagnosis with timely antibiotic

susceptibility results can prevent emergence and spread of resistance mechanism.

CONSENT

It is not applicable.

ETHICAL APPROVAL

Appropriate ethical approvals were taken before start of study. The study was done only on bacterial isolates obtained from samples received in the lab as part of routine patient care. No patient data was used in the study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Lee H, Lee H. Clinical and economic evaluation of multidrug-resistant *Acinetobacter baumannii* colonization in the intensive care unit. Infect Chemother. 2016;48(3):174-180.
   DOI: 10.3947/ic.2016.48.3.174.
   PubMed PMID: 27659440;
   PubMed Central PMCID: PMC5047998
2. Chang HH, Cohen T, Grad YH, Hanage WP, O'Brien TF, Lipsitch M. Origin and proliferation of multiple-drug resistance in bacterial pathogens. Microbiol Mol Biol Rev. 2015;79(1):101-16.
   DOI: 10.1128/MMBR.00039-14. Review.
   PubMed PMID: 25652543;
   PubMed Central PMCID: PMC4402963
3. Wyrsch ER, Roy Chowdhury P, Chapman TA, Charles IG, Hammond JM, Djordjevic SP. Genomic microbial epidemiology is needed to comprehend the global problem of antibiotic resistance and to improve pathogen diagnosis. Front Microbiol. 2016;7:843.
   DOI: 10.3389/fmicb.2016.00843. Review.
   PubMed PMID: 27379026;
   PubMed Central PMCID: PMC4908116
4. Patel J, Richter S. Mechanisms of resistance to antibacterial agents. In: Jorgensen J, Pfaller M, Carroll K, Funke G, Landry M, Richter S, Warnock D, editors. Manual of Clinical Microbiology. 11th ed. ASM Press, Washington, DC. 2015;1212-1245.
5. Opal SM, Medeiros AA. Molecular mechanisms of antibiotic resistance in bacteria. In: Mandell GL, Bennett JE and Dolin R, editors. Principles and Practice of Infectious Diseases, 6th ed. Philadelphia, PA; Elsievier Churchill, Livingstone Inc. 2005;1:253-270.
6. Weldhagen GF. Integrons and beta-lactamases--a novel perspective on resistance. Int J Antimicrob Agents. 2004;23(6):556-62. Review. PubMed PMID: 15194125
7. Crichton, Pamela B. *Enterobacteriaceae*: *Escherichia*, *Klebsiella*, Proteus and other genera. In: Collee JG, Fraser AC, Marmion BP, Simmons A, editors. Mackie and McCartney practical medical microbiology. 14th ed. New Delhi: Churchill Livingstone. 1996;361-84.
8. Clinical and Laboratory Standards Institute (CLSI). Performance standards for antimicrobial susceptibility testing. Twenty-Fifth Informational Supplement. M100-S24; 2015.
9. Sinha M, Srinivasa H, Macaden R. Antibiotic resistance profile & extended spectrum beta lactamase (ESBL) production in *Acinetobacter* species. Indian J Med Res. 2007;126(1):63-7. PubMed PMID: 17890826
10. Kumar MS, Lakshmi V, Rajagopalan R. Occurrence of extended spectrumbeta-lactamases among *Enterobacteriaceae* spp. isolated at a tertiary careinstitute. Indian J Med Microbiol. 2006;24(3):208-11. PubMed PMID: 16912442
11. Laghawe A, Jaitly N, Thombare V. The simultaneous detection of the ESBL and the AmpC b-lactamases in gram negative bacilli. J Clin Diagn Res. 2012;6:660–63.
12. Sid Ahmed MA, Bansal D, Acharya A, Elmi AA, Hamid JM, Sid Ahmed AM, et al. Antimicrobial susceptibility and molecular epidemiology of extended-spectrumbeta-lactamase-producing *Enterobacteriaceae* from intensive care units at Hamad Medical Corporation, Qatar. Antimicrob Resist Infect Control. 2016;5:4.
    DOI: 10.1186/s13756-016-0103-x
    PubMed PMID: 26865975;
    PubMed Central PMCID: PMC4748476
13. Bandekar N, Vinodkumar CS, Basavarajappa KG, Prabhakar PJ, Nagaraj P. The betalactamases mediated resistance amongst the gram negative bacilli in burn infections. Int J of Bio Res. 2011;2:766-70.
14. Harakuni S, Karadesai SG, Mutnal MB, Metgud SC. Prevalence of extended spectrum β-lactamase-producing clinical

isolates of *Klebsiella pneumoniae* in intensive care unit patients of a tertiary care hospital. Ann Trop Med Public Health. 2011;4:96-8.

15. Zhanel GG, DeCorby M, Laing N, Weshnoweski B, Vashisht R, Tailor F, et al. Antimicrobial-resistant pathogens in intensive care units in Canada: Results of the Canadian National Intensive Care Unit (CAN-ICU) study, 2005-2006. Antimicrob Agents Chemother. 2008;52(4):1430-7. DOI: 10.1128/AAC.01538-07
PubMed PMID: 18285482;
PubMed Central PMCID: PMC2292546
16. Ashrafian F, Askari E, Kalamatizade E, Ghabouli Shahroodi MJ, Naderi-Nasab M. The frequency of extended spectrum beta lactamase (ESBL) in *Escherichia coli* and *Klebsiella pneumoniae*. J Med Bacteriol. 2013;2(1-2):12-9.
17. Rath S, Dubey D, Sahu MC, Debata NK, Padhy RN. Surveillance of ESBL producing multidrug resistant *Escherichia coli* in a teaching hospital in India. Asian Pac J Trop Dis. 2014;4(2):140–49.
18. Shanthi M, Sekar U. Extended spectrum beta lactamase producing *Escherichia coli* and *Klebsiella pneumoniae*: Risk factors for infection and impact ofresistance on outcomes. J Assoc Physicians India. 2010;58Suppl:41-4. PubMed
PMID: 21568008
19. Chauhan K, Pandey A, Asthana AK, Madan M. Evaluation of phenotypic tests fordetection of *Klebsiella pneumoniae* carbapenemase and metallo-beta-lactamase inclinical isolates of *Escherichia coli* and *Klebsiella* species. Indian J PatholMicrobiol. 2015;58(1):31-5.
DOI: 10.4103/0377-4929.151168. PubMed PMID: 25673588
20. Wattal C, Goel N, Oberoi JK, Raveendran R, Datta S, Prasad KJ. Surveillance ofmultidrug resistant organisms in tertiary care hospital in Delhi, India. J Assoc Physicians India. 2010;58Suppl:32-6. Review.
PubMed PMID: 21563611.
21. Gupta E, Mohanty S, Sood S, Dhawan B, Das BK, Kapil A. Emerging resistance to carbapenems in a tertiary care hospital in north India. Indian J Med Res. 2006; 124(1):95-8. PubMed
PMID: 16926463
22. Sumita Y, Fukasawa M. Meropenem resistance in *Pseudomonas aeruginosa*. Chemotherapy. 1996;42(1):47-56. PubMed PMID: 8751266
23. Pragasam AK, Sahni RD, Anandan S, Sharma A, Gopi R, Hadibasha N, et al. A pilot study on carbapenemase detection: Do we see the same level of agreement as with the CLSI observations. J Clin Diagn Res. 2016;10(7):DC09-13.
doi: 10.7860/JCDR/2016/16417.8152
PubMed PMID: 27630840;
PubMed Central PMCID: PMC5020186
24. Tzouvelekis LS, Markogiannakis A, Psichogiou M, Tassios PT, Daikos GL. Carbapenemases in *Klebsiella pneumoniae* and other *Enterobacteriaceae*: An evolvingcrisis of global dimensions. Clin Microbiol Rev. 2012;25(4):682-707.
doi: 10.1128/CMR.05035-11. Review.
PubMed PMID: 23034326;
PubMed Central PMCID: PMC3485753
25. Jayol A, Poirel L, Dortet L, Nordmann P. National survey of colistin resistance among carbapenemase-producing *Enterobacteriaceae* and outbreak causedby colistin-resistant OXA-48-producing *Klebsiella pneumoniae*, France, 2014. Euro Surveill. 2016;21:37.
DOI: 10.2807/1560-7917.ES.2016.21.37.30339
PubMed PMID: 27685838;
PubMed Central PMCID: PMC5032854.
26. Reffert JL, Smith WJ. Fosfomycin for the treatment of resistant gram-negative bacterial infections. Insights from the society of infectious diseases pharmacists. Pharmacotherapy. 2014;34(8):845-57.
doi: 10.1002/phar.1434. Review.
PubMed PMID: 24782335

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